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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/603,231	06/26/2000	Han-Cheng Zhang	ORT-1236	3016

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EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/603,231	Zhang
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Feb 20, 2003* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *Feb 20, 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☐ Applicant's reply has overcome the following rejection(s): _____

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See attached sheet.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____

Claim(s) objected to: _____

Claim(s) rejected: _____

Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

10. ☐ Other:

Claims 1-8, 10, and 11 are rejected under 35 U.S.C. 103 (a) over Forbes et al. (PCT International Publication Number WO 93/18026) (September 16, 1993) over Hoekstra et al. (U.S. Patent 6,017,890) (January 25, 2000).

Forbes et al teach a compound of the formula (I) with all the limitations of claims 1-8 but devoid of A1 and A2, which are D- or L- amino acids selected from arginine, serine, leucine or phenyl alanine. (Abstract and page 1, lines 25-30, and page 2, line 1 to page 14, line 23).

Forbes et al also teach a pharmaceutically acceptable salts thereof (Abstract and claims 33, 36 and 37).

Forbes et al do not teach a compound with A1 and A2, which are D- or L- amino acids selected from arginine, serine, leucine or phenyl alanine.

Hoekstra et al. teach a compound with A1 and A2, which are D- or L- amino acids selected from arginine, serine, leucine or phenyl alanine (Column 1, lines 8-35 and Claim 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the A1 and A2, which are D- or L- amino acids selected from arginine, serine, leucine or phenyl alanine of Hoekstra et al. in the compound of the formula (I) with all the limitations of claims 1-8 but devoid of A1 and A2, which are D- or L- amino acids selected from arginine, serine, leucine or phenyl alanine of Forbes et al. since Hoekstra et al. states, "Hence, antagonists of the thrombin receptor based on SFLLRN are useful in antagonizing these protease-activated receptors and as such may be used to treat platelet mediated thrombotic disorders such as myocardial infarction, stroke, restenosis, angina, atherosclerosis, and ischemic attacks by virtue of their ability to prevent platelet aggregation (Column 1, lines 29-35)." An ordinary practitioner would have been motivated to combine and substitute the A1 and A2, which are D- or L- amino acids selected from arginine, serine, leucine

or phenyl alanine of Hoekstra et al. in the compound of the formula (I) with all the limitations of claims 1-8 but devoid of A1 and A2, which are D- or L- amino acids selected from arginine, serine, leucine or phenyl alanine of Forbes et al. in order to achieve the express advantages, as noted by Hoekstra et al, of antagonists of the thrombin receptor based on SFLLRN which are useful in antagonizing these protease-activated receptors and as such may be used to treat platelet mediated thrombotic disorders such as myocardial infarction, stroke, restenosis, angina, atherosclerosis, and ischemic attacks by virtue of their ability to prevent platelet aggregation.

Applicant's arguments filed on February 20, 2003, have been fully considered but they are not persuasive.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant then argues the 103 rejection is improper because it lacks a reasonable expectation of success.

With regard to the " lacks a reasonable expectation of success." argument, The MPEP 2143.02 states, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart , 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters

in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also Amgen, Inc. v. Chugai Pharmaceutical Co ., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied , 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022, 1023.); In re O'Farrell , 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.)."

There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Hoekstra et al. reference of the enabling methodology, the suggestion to modify the prior art, and evidence that a number of different compounds with A1 and A2, which are D- or L- amino acids selected from arginine, serine, leucine or phenyl alanine were actually experimentally studied and found to be functional (Column 1, lines 8-35 and Claim 1). This evidence of functionality trumps the attorney arguments, which argues that Hoekstra et al. reference is an invitation to research, since Hoekstra et al. steps beyond research and shows the functional product.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Hoekstra et al provides strong motivation as Hoekstra et al. states, "Hence, antagonists of the thrombin receptor based on SFLLRN are useful in antagonizing these protease-activated receptors and as such may be used to treat platelet mediated thrombotic disorders such as myocardial infarction, stroke, restenosis, angina, atherosclerosis, and ischemic attacks by virtue of their ability to prevent platelet aggregation (Column 1, lines 29-35)."

In response to applicant's argument that the applicant has an advantage other than the references cited in the office action, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

In response to applicant's argument that the compound of the claimed invention have PAR-1 activity against other serotonin receptors whereas Forbes reference teaches 5-HTIC receptor antagonist, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of

performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Applicant argues that Forbes reference does not teach the R1 and R3 substituents of the claimed invention. Applicant argues that the specific substituents of Forbes reference (C1-C6 alkyl) is different than the (CH2)m attached to a arC1-C8 alkyl of the claimed invention.. Applicant argues that because Forbes has a preferred embodiment of C1-C6 alkyl, Forbes is limited to the preferred embodiment. This argument is not persuasive. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Forbes has a preferred embodiment, this embodiment does not prevent the reference from suggesting broader embodiments in the disclosure and that this does not constitute a teaching away. Although Forbes reference uses C1-C6 alkyl at R1 and R3 positions, the property of substituting (CH2)m attached to a arC1-C8 alkyl at these positions is inherently present in this chemically and structurally identical molecule. For example, Forbes teaches that suitable alkyloxycarbonyl groups can be inserted in the R1 position by the conventional reaction process (Page 7, lines 14-30). Moreover, MPEP 2111 states, "Claims must be given their broadest reasonable interpretation. During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification". Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the examiner

reduces the possibility that the claim, once issued, will be interpreted more broadly than it is justified. *In re Prater,* 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)". In this case, any typical N-protecting groups can be substituted at the R1 and R3 position as explicitly suggested by Forbes.

Therefore, all the rejections made in the last office action are hereby properly maintained.

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